The Effect of α-Tocopherol and β-Carotene Supplementation on Colorectal Adenomas in Middle-Aged Male Smokers[1]

Nea Malila,[2] Jarmo Virtamo, Mikko Virtanen, Demetrius Albanes, Joseph A. Tangrea, and Jussi K. Huttunen

Department of Nutrition, National Public Health Institute, FIN-00300 Helsinki, Finland [N. M., J. V., M. V., J. K. H.], and Division of Clinical Sciences, National Cancer Institute, NIH, Bethesda, Maryland 20892 [D. A., J. A. T.]

Abstract

Epidemiological and experimental studies have indicated that dietary factors such as vitamin C, vitamin E, and β-carotene are associated with the risk of colorectal cancer. This study was carried out within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study), whose participants were randomly assigned to four supplementation groups: (*a*) α-tocopherol (AT), 50 mg/day; (*b*) β-carotene (BC), 20 mg/day; (*c*) both AT and BC; and (*d*) placebo. We included the 15,538 ATBC Study participants who had been randomized within the areas of three major cities in southern Finland. Cases of colorectal adenoma ($n = 146$) were identified by the pathology laboratories in the study areas, and these participants' medical records were collected and reviewed. α-tocopherol supplementation increased the risk for adenomas (relative risk, 1.66; 95% confidence interval, 1.19–2.32), whereas β-carotene supplementation had no effect on the risk (relative risk, 0.98; 95% confidence interval, 0.71–1.35). Slightly more prediagnosis rectal bleeding and intestinal pain occurred in those adenoma cases who received α-tocopherol supplements than in those who did not. Thus, some bias may have resulted, with α-tocopherol supplementation leading to more colonoscopies and, thus, to an increased detection of incident polyps in this group. This is further supported by the trial finding that α-tocopherol supplementation did not increase the risk of colorectal cancer.

Introduction

It is generally accepted that colorectal adenomas are precursors for most colorectal cancers. This adenoma-carcinoma sequence is probably a multistep process, offering the possibility to prevent colorectal cancer in the benign adenoma phase. (1) Age, gender, genetic predisposition, and the use of nonsteroidal anti-inflammatory drugs are associated with colorectal cancer and adenomatous polyps (2, 3); there is also evidence that diets high in vegetables are inversely associated with the risk for colorectal cancer, and the high consumption of alcohol and red meat is positively associated with the risk (3).

Several clinical trials have tested the ability of antioxidant vitamins to prevent colorectal adenomas, but results have been inconsistent (4–10). When the effect of ascorbic acid (3 g/day) was studied in 49 patients with polyposis coli, the results after 9 months' follow-up suggested a reduction both in number and in area of rectal polyps (7). However, in two other trials, combinations of ascorbic acid and α-tocopherol supplementation had no effect on adenoma recurrence (4, 6). A trial with three treatment regimes: (*a*) vitamins A, C, and E combined; (*b*) lactulose; and (*c*) no treatment, suggested a significant reduction in adenoma recurrence in the two active groups (5), but a large trial testing β-carotene alone or vitamins C and E combined showed no effect on adenoma recurrence (8). Likewise, in the Australian Polyp Prevention Project, no significant reduction was observed in the number of new adenomas with β-carotene supplementation (9). In another trial, no effect was found for β-carotene, vitamins C and E, and selenium combined in preventing adenoma recurrence or growth (10).

We report here the effect of α-tocopherol and β-carotene supplementation on the incidence of colorectal adenomas in middle-aged male smokers participating in the ATBC Study,[3] a controlled trial to examine the effects of α-tocopherol and β-carotene supplementation on cancer.

Materials and Methods

This study was done within the ATBC Study, a randomized, double-blind, placebo-controlled, 2×2 factorial trial (11). Participants were recruited from the total male population, ages 50–69 years, of Southwestern Finland ($n = 290{,}406$) and had to be current smokers (five or more cigarettes daily) at study entry. Before randomization, the participants completed questionnaires about medical, dietary, and smoking histories, their height and weight was measured, and a serum sample was taken. The dietary intake of α-tocopherol and β-carotene was estimated from a dietary history questionnaire (12), while serum concentrations of α-tocopherol and β-carotene were determined by high-performance liquid chromatographic analyses (13). The recruitment took place from 1985 to June 1988, and a total of 29,133 men were randomly assigned to one of four intervention groups: α-tocopherol (AT) alone 50 mg/day, β-carotene (BC) alone 20 mg/day, both AT and BC, or placebo.

Each participant visited his local study center three times

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[2] To whom requests for reprints should be addressed, at National Public Health Institute, Department of Nutrition, Mannerheimintie 166, FIN-00300 Helsinki, Finland.

[3] The abbreviations used are: ATBC Study, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; RR, relative risk; CI, confidence interval.

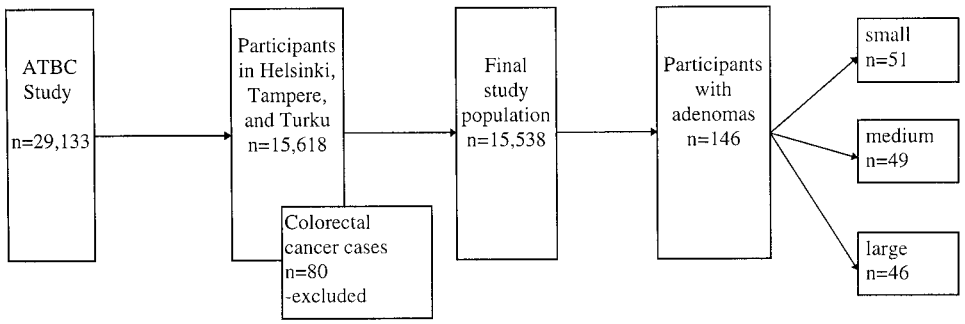

Fig. 1. Participants of the adenoma study.

annually. At each visit he reported about medical contacts and symptoms experienced since the last visit; these included a structured list of 30 symptoms, among them gastrointestinal symptoms, nose-bleeds, and bruises. At each visit the old trial capsule pack was exchanged for a new one. Study compliance was estimated by the total number of capsules used divided by the number of study-days. Four of five participants took more than 95% of their capsules during the trial, with compliance similar across supplementation groups.

Study Cohort. The present study was limited to the 15,618 ATBC Study participants of the cities of Helsinki, Tampere, and Turku and their surroundings, areas chosen because each had a large university hospital and participants residing in both urban and rural surroundings. Data collecting in these areas was manageable: only two pathology laboratories made all of the histological diagnoses within the areas of Turku and of Tampere each, and the laboratories of Helsinki and surroundings were conveniently close. Those participants (n = 79) with colorectal cancer diagnosed during the time-frame of this study were excluded, as was one with cancer found within a colonic adenoma before randomization, which left 15,538 participants for analysis (Fig. 1). None of these excluded cancer cases had had an adenoma diagnosed before their cancer diagnoses within the trial. Participants of this study were evenly distributed into the four supplementation groups. Follow-up time was on average 6.3 years (SD, 1.4), and drop-out rate was 32% in all of the supplementation groups.

Case Assessment and Data Collection. Each case was identified at one of the pathology laboratories located within the study areas using the unique personal identification number (a national identifier) of each ATBC Study participant. For each case of colonic or rectal adenoma, the pathology report was obtained and hospital medical records were collected and reviewed, furnishing data on symptoms preceding the detection of adenomas, their location, number, and histology, and size of the largest adenoma. Any use of nonsteroidal anti-inflammatory drugs at the time of diagnosis was recorded both from hospital patient records and the study participant cards.

Each university hospital for each city had a computerized system from nearly the beginning of the ATBC Study; in other laboratories, data were collected manually for the 1980s and in part for the early 1990s, making the 1980s data less complete than in the 1990s with computerized systems; this is, however, not related to the intervention assignment.

Statistical Analyses. The end point of this study was the first adenoma (tubular, tubulovillous, or villous) diagnosed after randomization. Follow-up for each of the 146 cases with adenomas started from the day of randomization and ended at death, diagnosis of an adenoma, or by April 30, 1993, at the latest.

In all of the analyses, the intention-to-treat principle was used, with all of the subjects being allocated to the supplementation arm as randomized. The RR for adenoma incidence by supplementation was calculated by the Cox proportional hazards model. The interaction between α-tocopherol and β-carotene supplementation was tested by including the main effects in the model simultaneously and then adding their cross-product interaction term. Interactions between α-tocopherol/β-carotene supplementation and baseline serum α-tocopherol/β-carotene concentration, as well as baseline dietary intake of α-tocopherol/β-carotene, were also tested by first entering the main effects into the model and then adding their cross-product term. Kaplan-Meier cumulative incidence curves were plotted for the two supplementation groups separately, and two-sided nominal Ps were derived from the unweighted log-rank statistic. Analysis of cases after 1 year of follow-up (n = 126) excluded all of the follow-up times under 1 year.

Results

No essential differences appeared between the supplementation groups in medians of the following baseline characteristics: age, body mass index, total energy, calcium, vitamin D and alcohol intake, total years of smoking, dietary intake of α-tocopherol and β-carotene, and baseline serum value of α-tocopherol and β-carotene (Table 1).

The incidence of self-reported symptoms (nose-bleeds, bruises, gastrointestinal symptoms) during the previous 4-month period did not differ between supplementation groups at baseline or later during the study among the participants still in the study.

Characteristics and Location of Adenomas. Of the 146 cases, only rectal adenomas were found in 33% (n = 48), and only colonic adenomas in 41% (n = 60). Six cases had ten or more simultaneous adenomas in the large bowel, whereas in most cases (89%, n = 130) the number of adenomas varied between one and four at a time. Eleven cases had been diagnosed with some type of polyp before the trial, and four had had a hyperplastic polyp diagnosed during the trial before the adenoma. In 35% of the cases (n = 51), the largest adenoma was small (under 5 mm in diameter); in 34% (n = 49), medium-size (from 5 to 9 mm); and in 31% (n = 46), large (1 cm or over). In most cases (90%, n = 131), the adenomas were histologically only tubular; and in 10% (n = 15), tubulovillous adenomas were also found; no villous adenomas were detected. All of the tubulovillous adenomas were medium (n = 6) or large (n = 9) in size.

RRs for Adenomas by Supplementation. Of the 146 cases with adenomas, 47 were in the group receiving α-tocopherol only, 44 in the α-tocopherol and β-carotene group, 28 in the

Table 1 Median baseline characteristics of the study population (n = 15,538) in the four supplementation groups

	α-tocopherol (n = 3,890)	α-tocopherol and β-carotene (n = 3,878)	β-carotene (n = 3,883)	Placebo (n = 3,887)
Age (years)	57.0	57.2	57.0	56.7
BMI[a] (kg/m^2)	25.8	25.8	25.7	25.8
Smoking years	37.0	36.0	37.0	36.0
Serum AT (mg/l)	11.8	11.8	11.8	11.7
Serum BC (μg/l)	172	174	176	177
Dietary AT (mg/day)	11.0	11.1	11.1	10.9
Dietary BC (mg/day)	1.73	1.77	1.76	1.77
Dietary vitamin D (μg/day)	4.88	4.81	4.98	4.85
Calcium intake (g/day)	1.31	1.29	1.30	1.30
Total energy intake (kcal/day)	2704	2688	2687	2686
Alcohol intake (g/day)	12.3	12.0	12.1	11.6

[a] BMI, body mass index; AT, α-tocopherol; BC, β-carotene.

β-carotene only group, and 27 in the placebo group. The risk for adenomas was significantly higher (RR, 1.66; 95% CI, 1.19–2.32) in those receiving α-tocopherol supplementation than in those not receiving it, whereas β-carotene supplementation had no effect on risk (RR, 0.98; 95% CI, 0.71–1.35). Eliminating the 1st year of follow-up reduced the effect of α-tocopherol supplementation slightly (RR, 1.48; 95% CI, 1.04–2.11), whereas the effect of β-carotene supplementation remained unchanged (RR, 0.97; 95% CI, 0.69–1.38). Fig. 2 shows the Kaplan-Meier curves for the cumulative incidence of adenomas during intervention with α-tocopherol *versus* no α-tocopherol and with β-carotene *versus* no β-carotene supplementation. There was no interaction between α-tocopherol and β-carotene supplementation effects on risk for adenomas (P = 0.75). Neither was there any interaction between the effects of α-tocopherol supplementation and baseline serum α-tocopherol concentration (P for interaction, 0.52) or dietary intake of α-tocopherol (P for interaction, 0.13), or between β-carotene supplementation and baseline serum β-carotene concentration (P for interaction, 0.91) or its dietary intake (P for interaction, 0.47).

These results did not change when the 15 cases with a prior history of polyps were excluded from analyses (RR, 1.63; 95% CI, 1.14–2.32 for α-tocopherol supplementation *versus* no α-tocopherol; RR, 0.96; 95% CI, 0.60–1.81 for β-carotene supplementation *versus* no β-carotene). Results remained unchanged also when all of the cases were excluded who reported use of nonsteroidal anti-inflammatory drugs at the time of diagnosis (n = 15; RR, 1.68; 95% CI, 1.18–2.40 for α-tocopherol *versus* no α-tocopherol; RR, 0.93; 95% CI, 0.66–1.31 for β-carotene *versus* no β-carotene).

Prediagnosis Symptoms. As to symptoms recorded before the detection of adenomas and possible interaction with supplementation, of the 146 adenoma cases, 69 cases had prediagnosis rectal bleeding and 74 did not (data lacking for 3 cases). In 12 cases, bleeding was classified as melena (8 in the α-tocopherol groups, 4 in the no α-tocopherol groups); and others had blood in the feces or a positive fecal blood test. Some degree of rectal bleeding occurred in 49% (45 of 91) of the adenoma cases on α-tocopherol supplementation and in 44% (24 of 55) of those receiving no α-tocopherol (P = 0.48). Corresponding figures for those receiving and not receiving β-carotene supplementation were 47% (34 of 72) and 47% (35 of 74; P = 0.94). Other symptoms (not mutually exclusive) preceding the detection of adenomas were diarrhea (22 cases), constipation (23 cases), intestinal pain (42 cases), and change in bowel function (17 cases). Prediagnostic intestinal pain was reported by 32% (29 of 91) of those receiving α-tocopherol and by 24% (13 of 55) by those receiving none (P = 0.32). Corresponding figures for those receiving and not receiving β-carotene were 25% (18 of 72) and 32% (24 of 74; P = 0.61). Both bleeding and intestinal

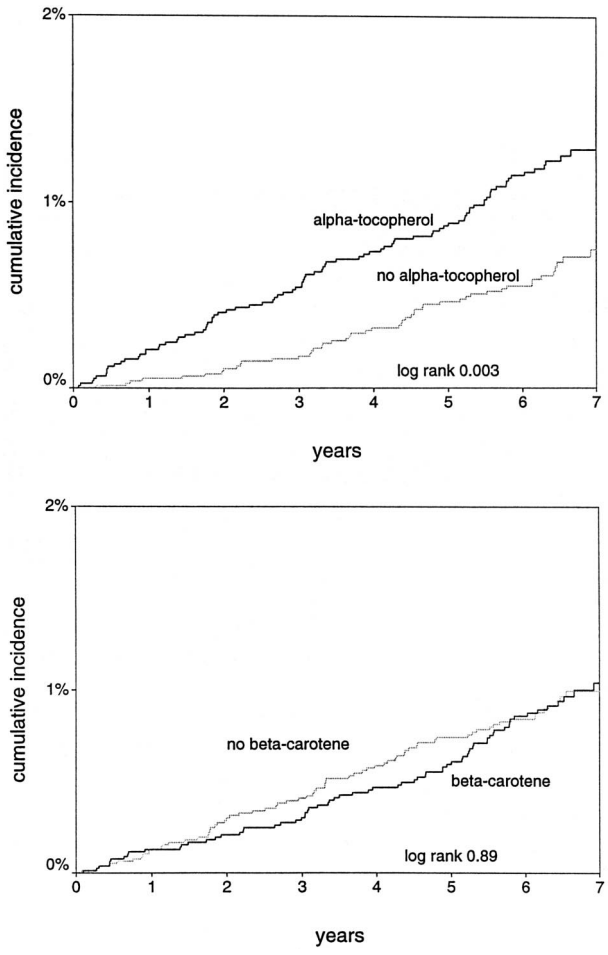

Fig. 2. Kaplan-Meier cumulative incidence curves for α-tocopherol *versus* no α-tocopherol and for β-carotene *versus* no β-carotene supplementation.

pain was reported in 16 cases before diagnosis, 13 of them receiving α-tocopherol and 3 not. Other symptoms were reported similarly among cases with different supplementations.

Discussion

In this study of 15,538 middle-aged male smokers we found an increased risk for colorectal adenomas in the group receiving α-tocopherol supplementation compared with the no-α-tocopherol group. Because the study population was not screened for colorectal polyps before the study, and no systematic screening was performed later during the trial, we probably observed only a small proportion of the polyps in the population. The prevalence for colorectal polyps varies from 10 to 50% in the populations studied, with the prevalence of adenomas estimated to be about 10% in Finnish men (14). Because we identified the adenomas from the files of the pathology laboratories, we had data also on adenomas of the trial drop-outs.

The possibility that the trial supplements affected the diagnosis of adenomas must be considered in interpreting these findings. α-tocopherol supplementation may have caused gastrointestinal symptoms such as intestinal pain, constipation, change in bowel function, or rectal bleeding; and these could have affected the referrals for colonoscopies. Our data give some support to increased incidence of rectal bleeding and intestinal pain among the adenoma cases receiving α-tocopherol supplementation, although the difference was not significant. Moreover, the rapid effect on the higher incidence of adenomas after starting α-tocopherol supplementation also supports the possibility of bias in the detection of adenomas. α-tocopherol has been found to inhibit platelet aggregation and release *in vitro* and platelet adhesion *in vivo* (15), but the doses at which this effect has been shown to occur have been ≥200 IU/day.

Vitamin E supplements reduce the incidence of chemical- and radiation-induced cancer in animal and *in vitro* models (16). In addition, vitamin E has been connected to cell proliferation and differentiation (17). Epidemiological studies have provided evidence, although not consistently, that suggest an inverse association between dietary intake of vitamin E or serum concentration of α-tocopherol and the risk for cancer (18–20). A pooled analysis on five cohorts suggested that serum α-tocopherol concentration may be inversely related to the risk for colorectal cancer, but the association was modest, CIs were wide, and the test for trend was nonsignificant (21). In controlled intervention studies, the effect of α-tocopherol supplementation has varied from no effect to a significant reduction in cancer incidence. In the ATBC Study, supplementation with α-tocopherol had no effect on lung cancer incidence (22) but reduced significantly the incidence of prostate cancer by 32% (23); in colorectal cancer incidence, a nonsignificant reduction of 16% was observed (24). In Linxian, China, an intervention with a combination of β-carotene, vitamin E, and selenium resulted in lower cancer rates and in a significant reduction in stomach cancer mortality (25).

We found no effect for β-carotene supplementation on colorectal adenomas, in line with earlier adenoma supplementation studies as well as with large controlled trials showing no effect for β-carotene on the incidence of colorectal cancer (24, 26, 27).

In summary, for our middle-aged male smokers who took supplements of α-tocopherol and β-carotene, the incidence of colorectal adenomas was significantly increased in the α-tocopherol group compared with that of those of no α-tocopherol. β-carotene supplementation had no effect on the incidence of adenomas in our study. However, we suspect bias in the diagnostic process: supplementation with α-tocopherol may have caused more rectal bleeding and intestinal pain leading to more colonoscopies and, thus, an increase in the incidence of polyps detected. Still, a true effect cannot be completely ruled out inasmuch as our data on bleeding or other symptoms that preceded the diagnosis cannot fully explain the increased incidence of adenomas in the α-tocopherol group. The risk of colorectal cancer was not increased in the participants of the ATBC Study receiving α-tocopherol supplementation, which supports detection bias. A posttrial follow-up seems warranted to confirm this suspicion and to clarify any possible long-term effects of these supplements.

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